REMARKS/ARGUMENTS

I. Status of the claims

With entry of this Amendment, claims 95 and 106 are amended. Claims 95-107 are currently pending. Claims 99, 102, 104 and 105 were withdrawn by the Examiner due to non-elected species. Claims 95-98, 100, 101, 103, 106 and 107 are being examined.

II. Support for the amendments

All amendments to the claims made in this amendment were made to correct obvious typographical errors. The Applicants have not made any substantive amendments in this paper. Accordingly, no new matter is added.

III. Information Disclosure Statement

The Examiner states that the information disclosure statement filed 8/16/2004 fails to comply with 37 CFR 1.98(a)(2), and that the copies of cited foreign patent documents and the non-patent literature publications are not found in the parent case 10/133,128.

On April 5, 2007, Applicants filed, in the present application, a Supplemental Information Disclosure Statement, Form PTO/SB/08 and copies of cited foreign patent documents and non-patent literature publications that were listed on the information disclosure statement filed 8/16/2004. Applicants respectfully request that each document listed on the Form PTO/SB/08 filed on April 5, 2007, be considered by the Examiner and be made of record in the present application, and that an initialed copy of that Form be returned in accordance with MPEP §609.

IV. Oath/Declaration

The Examiner asserts that the oath or declaration is defective because it does not identify the mailing address, city and either state or foreign country of residence of inventor Per-Ola Fresgard, and indicated that the missing information may be provided on either an application data sheet or supplemental oath or declaration.

Attached hereto is an application data sheet which includes the information requested by the Examiner.

V. Objections to the Claims

The Examiner objected to claim 106 because the word "domain" occurs twice in immediate succession in claim 106 on line 2 of the claim. The Applicants have amended claim 106 to delete the second occurrence of "domains" on line 2.

VI. Rejection under 35 U.S.C. § 112

The Examiner rejected claims 95-98, 100, 101, 103, 106 and 107 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner asserts that the phrase 'non-naturally-occurring amino acids sequences', present in claim 95, can be broadly interpreted to mean any amino acid sequences that do not occur in nature, or it can be narrowly interpreted to mean that the monomers have amino acid sequences that are not wild-type sequences (e.g. wild-type human LDL receptor A domain). In addition, the Examiner notes that Claim 93 [*sic*] also recites the limitation that the 'non-naturally occurring LDL- receptor class A monomer domain variants comprise' the amino acid sequence recited in SEQ ID NO. 331, asserts that SEQ ID NO. 331 encompasses the wild-type human LDL receptor A domain, and concludes that the limitation provided by SEQ ID NO. 331 is in "direct conflict" with the limitation provided by the phase 'non-naturally occurring', which, the Examiner alleges, creates confusion about the metes and bounds of the instant invention.

The Applicants respectfully traverse this rejection. Claim 95 reads:

> 95. A method for producing a polypeptide, said method comprising,
> expressing a nucleic acid encoding a polypeptide, thereby recombinantly expressing the polypeptide;
> wherein the polypeptide comprises a first LDL-receptor class A monomer domain variant and a second LDL-receptor class A monomer domain variant,
> wherein each of the first and second LDL-receptor class A monomer domain variants have non-naturally-occurring amino acid sequences,

wherein the first and second LDL-receptor class A monomer domain variants each have a binding specificity for a target molecule,

wherein the two domain variants are linked by a heterologous linker, and

wherein each of first and second the LDL-receptor class A monomer domain variants comprise the following sequence:

C-X(3-15)-C-X(4-15)-C-X(6-7)-C-[N,D]-X(3)-[D,E,N,Q,H,S,T]-C-X(4-6)-D-E-X(2-8)-C (SEQ ID NO:331).

To properly construe a claim, all the limitations of the claims must be considered and given weight (MPEP §2143.03). Multiple limitations in a claim typically serve to define from different perspectives subject matter falling within the claim. In the present case, the "conflicting" limitations alleged by the Examiner operate together to define the scope of the claimed invention. Specifically, the limitation "wherein each of the two variants have non-naturally-occurring amino acids sequences" means that each LDL-receptor class A monomer domain variant in a polypeptide produced by the claimed method has an amino acid sequence that is not found in nature *i.e.*, not found in a naturally-occurring LDL-receptor class A monomer domain. This limitation is separate from the limitation relating to SEQ ID NO:331. Therefore, although the sequence of a naturally-occurring LDL-receptor class A monomer domain determined from, *e.g.*, a portion of a wild-type LDL receptor, might fall within the sequence limitation of SEQ ID NO: 331, it would not be a "non-naturally-occurring amino acid sequence" and thus a method of producing a polypeptide comprising such a naturally-occurring LDL-receptor class A monomer domain would not be within the metes and bounds of Claim 95.

In view of the foregoing, the Applicants maintain that the claim language is clear both on its face and in view of the specification, and respectfully request withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

VII. Rejections under 35 U.S.C. § 102

The Examiner rejected claims 95, 100, 103, 106 and 107 under 35 U.S.C. §102(b) as anticipated by Esser, *et al.* (Journal of Biological Chemistry, Vol. 263: 13282-13290; 1988).

A. *The Present Invention*

Claim 95 is the only independent claim in the set of currently-pending claims in the present application. All other pending claims are dependent either on claim 95 or another dependent claim. Accordingly, the discussion below focuses on claim 95.

95. A method for producing a polypeptide, said method comprising,
expressing a nucleic acid encoding a polypeptide, thereby recombinantly expressing the polypeptide;
wherein the polypeptide comprises a first LDL-receptor class A monomer domain variant and a second LDL-receptor class A monomer domain variant,
wherein each of the first and second LDL-receptor class A monomer domain variants have non-naturally-occurring amino acid sequences,
wherein the first and second LDL-receptor class A monomer domain variants each have a binding specificity for a target molecule,
wherein the two domain variants are linked by a heterologous linker, and
wherein each of first and second the LDL-receptor class A monomer domain variants comprise the following sequence:
C-X(3-15)-C-X(4-15)-C-X(6-7)-C-[N,D]-X(3)-[D,E,N,Q,H,S,T]-C-X(4-6)-D-E-X(2-8)-C (SEQ ID NO:331).

B. *Esser, et al.*

Esser, *et al.*, teach a mutational analysis of the ligand binding domain of the low density lipoprotein (LDL) receptor. According to Esser, *et al.*, the ligand binding domain of the LDL receptor contains seven imperfect repeats of a 40-amino acid cysteine-rich sequence (referred to by Esser, *et al.*, as Repeats 1-7). To dissect the contribution of these different cysteine-rich repeats to ligand binding, Esser, *et al.*, used oligonucleotide-directed mutagenesis to generate nine substitution mutations (each as a separate construct) in the ligand binding domain. The changes relative to the native sequence for each of the nine mutant constructs are illustrated in Fig. 1 of Esser, *et al.* Three of the constructs have mutations in Repeat 1, five constructs have mutations in Repeat 5, and one construct has a mutation in Repeat 6. None of the mutant constructs have mutations in more than one Repeat.

C. *Analysis*

For anticipation under 35 U.S.C. §102, a single reference must teach every aspect of the claimed invention. The method of producing polypeptides encompassed by the claimed

invention requires that each produced polypeptide have at least *two (a first and second) LDL-receptor class A monomer domain variants, wherein each of the first and second LDL-receptor class A monomer domain variants have non-naturally-occurring amino acid sequences*, and wherein (*inter alia*) the two domain variants are linked by a heterologous linker. As described above, Esser, *et al.*, teach in relevant part nine substitution mutations in the ligand binding domain. Each of these nine substitution mutations occurs in a single Repeat: three occur in Repeat 1, five occur in Repeat 5, and one occurs in Repeat 6. None of these nine mutant constructs have mutations in more than one Repeat. Since each of the constructs containing mutations in the ligand binding domain taught by Esser, *et al.*, have mutations in only one Repeat, and the claimed invention requires each produced polypeptide to have at least two LDL-receptor class A monomer domains, each of which must have non-naturally-occurring sequences, the Applicants respectfully submit that Esser, *et al.*, do not anticipate the pending claims.

In view of the foregoing, the Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102.

VIII. Rejections under 35 U.S.C. § 103

The Examiner rejected claims 95-98, 100, 101, 103, 106 and 107 under 35 U.S.C. §103(a) as unpatentable over Esser, *et al.* (Journal of Biological Chemistry. Vol. 263: 13282-13290; 1988), in view of Bajari, *et al.*, (Biological Chemistry. Vol. 379: 10153-10162; 1998), and "if necessary", further in view of Russell, *et al.*, (Journal of Biological Chemistry. Vol. 264: 21682-21688; 1989), and Rudolph, *et al.* (The FASEB Journal. Vol. 10: p. 49-56; 1996).

A. The Present Invention

See above.

B. Esser, et al.

See above.

C. Bajari, et al.

Bajari, *et al.*, define the minimal binding domain of the multifunctional chicken oocyte receptor for yolk deposition (termed LR8), a relative of the low density lipoprotein

receptor (LDLR). Bajari, *et al.*, used phage display of fragments derived from the entire LR8 receptor molecule and panning on the ligand -- receptor associated protein (RAP) -- to define an 80 residue stretch LR8 minireceptor. The 80 residue stretch contains 12 cysteines, and represents parts of the second, the entire third, and parts of the fourth, of the eight clustered 'ligand binding repeats' in LR8. Bajari, *et al.*, state that in addition to its use in defining minimal binding domains, the phage display approach provides powerful tools for dissection, and consequently, manipulation, of the function of receptors so as to direct their binding activity toward ligands of diagnostic and/or therapeutic interest. The reference also teaches that the phage display method is adaptable to rapid analysis of in vitro mutagenized receptor fragments in order to obtain soluble minireceptors that may interact with a defined subset of ligands, and states that LR8 is an ideal substrate to perform such studies due to its being the smallest known member of the LDLR family that can bind all of the ligands of the family identified so far.

Bajari, *et al.*, do not teach any constructs or polypeptides comprising two or more LDL-receptor class A monomer domain variants, where the two domain variants are linked by a heterologous linker and each of the variants has non-naturally-occurring amino acid sequences.

D. *Russell, et al.*

Russell, *et al.*, assess the contribution of each of seven imperfect repeats of a 40-amino acid cysteine-rich sequence in the ligand binding domain of the low density lipoprotein (LDL) receptor via a series of site-directed mutations made individually in each repeat: 1) deletion of the repeat, 2) substitution of a conserved isoleucine with aspartic acid, and 3) substitution of a conserved aspartic acid with tyrosine. Each of the mutant constructs containing substitution mutations had a mutation in only a single repeat. None of the mutant constructs contained mutations in two or more repeats simultaneously.

E. *Rudolph, et al.*

Rudolph, *et al.*, teach that insoluble, inactive inclusion bodies (formed upon recombinant protein production in transformed microorganisms) can be isolated by solid/liquid separation. The reference discloses folding procedures for efficient in vitro reconstitution of complex hydrophobic, multidomain, oligomeric, or highly disulfide-bonded proteins. Rudolph,

et al., further note that modification of the protein sequence has been exploited to improve in vitro folding.

Rudolph, *et al.*, teach nothing about the LDL receptor or A-domains, indeed, Rudolph, *et al.*, teach nothing about any repeated domains having cysteine-rich sequences.

F. Analysis

As noted above, Esser, *et al.*, do not teach polypeptides comprising at least two non-naturally occurring LDL-receptor class A monomer domain variants, wherein each of the two variants have non-naturally-occurring amino acids sequences, and wherein (*inter alia*) the two domain variants are linked by a heterologous linker. This failing is not remedied by any of the secondary references cited by the Examiner. Neither Esser, *et al.*, nor any of Bajari, et al., Russell, et al., or Rudolph, et al., provide any motivation or suggestion (explicit or implicit) to arrive at the methods of the present invention.

As stated in the abstract of Esser, *et al.*, the studies performed therein were done "*[t]o dissect the contribution of these different cysteine-rich repeats to ligand binding*" by the human (native) LDL receptor (emphasis added). As detailed above, Esser, *et al.*, teach nine substitution mutations in the ligand binding domain, where each of the nine mutations occurs in a single Repeat; none of the nine mutant constructs taught by Esser, et al., have mutations in more than one Repeat.

Similarly, Russell, *et al.*, teach in relevant part seven substitution mutations where aspartic acid is substituted for a conserved isoleucine in each of the seven repeats. As in Esser, *et al.*, each of these mutant constructs contains only a single mutation – the first has the mutation in the first repeat, the second has it in the second repeat, and so on for all seven repeats. Russell, *et al.*, further teach another set of mutant constructs where a conserved Asp between the 5th and 6th cysteines is mutated, again on a repeat-by-repeat basis, to a Tyr. As above, none of the mutant constructs containing the Asp-to-Tyr mutation has the mutation in two or more repeats simultaneously. Furthermore, the Asp mutated by Russell, *et al.*, is required by the SEQ ID NO:331 sequence limitation of the claimed invention; the constructs containing the Asp-to-Tyr mutation fall outside of this sequence limitation.

Generating mutant constructs with point mutations in one or another of the Repeats, as done by Esser, *et al.*, and Russell, *et al.*, is presumably a scientifically-preferred method for determining the contributions to ligand binding of the different repeats. If either Esser, *et al.*, or Russell, *et al.*, had generated constructs having multiple mutations simultaneously in different repeats, the results would likely have been considerably more difficult to interpret (*e.g.*, did altered binding result from mutations in Repeat *x* or from mutations in Repeat *y*?). Taken together, the collective guidance from both references thus seems to be that if any subsequent researchers wish to further dissect contributions of the sequences of different cysteine-rich repeats to ligand binding in the native LDL receptor (or indeed, in any naturally-occurring protein containing LDL-receptor class A monomer domains), such researchers should make mutations in one repeat at a time, and not multiple repeats simultaneously as is required by the methods of the present invention.

Bajari, *et al.*, teach a different approach from that of Esser, *et al.*, or Russell, *et al.*, to the analysis of the ligand binding regions of A-domain-containing receptors – rather than making individual point mutations in the ligand binding domain (or deleting specified regions thereof), Bajari, *et al.*, randomly generate fragments of the entire receptor protein and use phage display to identify those fragments that have ligand binding activity. The constructs taught by Bajari, *et al.*, thus presumably do not contain LDL-receptor class A monomer domain variants having *non-naturally*-occurring amino acid sequences, although they do contain fragments of LDL-receptor class A monomer domain variants having *naturally*-occurring amino acid sequences. However, such fragments do not satisfy the sequence requirements of SEQ ID NO: 331 because SEQ ID NO: 331 defines a complete LDL-receptor class A monomer domain, and not a fragment thereof.

As indicated above, Bajari, *et al.*, teach that the phage display method is adaptable to rapid analysis of in vitro mutagenized receptor fragments in order to obtain soluble minireceptors that may interact with a defined subset of ligands, and states that LR8 is an ideal substrate to perform such studies due to its being the smallest known member of the LDLR family that can bind all of the ligands of the family identified so far. The Applicants note that

this teaching is directed to the analysis of mutagenized receptor fragments of *a particular selected member* of the LDLR family ("...LR8 is an ideal substrate to perform such studies..."). Nothing in Bajari, *et al.*, can fairly be said to suggest the making of the polypeptides as claimed by the present invention, where such polypeptides are generated based not on any particular member of the LDLR family, but rather on a consensus sequence provided by the Applicants.

The reference of Rudolph, *et al.*, teaches nothing about any repeated domains having cysteine-rich sequences (the LDL receptor, A-domains or otherwise), and is therefore not address any further in this paper.

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so. *In re Kahn*, 441 F.3d 977, 986 (Fed. Cir. 2006). Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. *Id.* at 988. In the present case, the Examiner has not articulated any reasoning or rationale to combine any of the teachings of Bajari, *et al.*, Russell, *et al.*, or Rudolph, *et al.*, with Esser, *et al.*, to arrive at the claimed invention, or to support the Examiner's conclusion of obviousness.

In view of the foregoing, the Applicants respectfully request withdrawal of the rejection(s) under 35 U.S.C. §103.

IX. Double Patenting

The Examiner provisionally rejected claim 95-98 and 103 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 21, 22, 24, 25 and 31 of copending Application No. 10/971,679, filed 10/22/2004.

The present application was filed on 10/24/2003. Where a provisional nonstatutory obviousness-type double patenting rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application may be rejectable on other grounds, the MPEP (§804) instructs the Examiner to withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. Accordingly, the

Applicants respectfully request the Examiner to withdraw this provisional nonstatutory obviousness-type double patenting rejection and allow this application to issue.

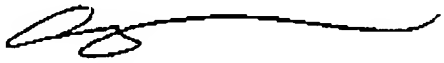
CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 650-244-3147.

The Commissioner is hereby authorized to charge any additional fees which may be required or credit any overpayment to Deposit Account No. 01-0519 in the name of Amgen Inc.

Respectfully submitted,



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